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Evaluation of the measurement of tendon and ligament thicknesses and the presence of enthesitis in lower extremities in female patients with acne vulgaris: a randomized controlled trial

Akne vulgarisli kadın hastalarda tendon ve bağ kalınlıkları ölçümünün ve alt ekstremitelerde entezit varlığının değerlendirilmesi: randomize kontrollü bir çalışma

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ABSTRACT

Aim: Acne Vulgaris (AV) is a multifactorial disease which affects young population and is most common in adolescents. There are no studies in the literature invastigating the presence of enthesitis and lower extremity tendons and ligaments thicknesses in patients with AV. To investigate the presence of enthesitis and to evaluate the tendon and ligament thicknesses in lower extremities in patients with AV.

Material and Method: Thirty patients with a diagnosis of AV and 18 healthy participants, were included. Acne severity was determined with the Global Acne Grading System (GAGS). A single radiologist performed ultrasonographic evaluation with respect to Glasgow Ultrasonographic Enthesitis Scoring System (GUESS). Measurement were done on quadriceps tendons, patellar tendons, Achilles tendons and plantar fascias of the bilaterally lower extremity.

Results: Age, body mass index, alcohol usage and smoking were similar between groups. GUESS score was similar in both group. Proximal patellar ligaments, distal patellar ligaments, Achilles tendons and plantar fascias thicknesses were significantly increased in dominant and non-dominant legs in patients with AV ($p<0.05$).

Conclusion: This study suggest that AV may lead to increase leg tendons and ligaments' thicknesses.

Keywords: Acne vulgaris, enthesitis, GUESS score

ÖZ

Amaç: Akne Vulgaris (AV), genç popülasyonu etkileyen ve en sık ergenlerde görülen multifaktöriyel bir hastalıktır. Literatürde AV'li hastalarda entezit varlığını ve alt ekstremite tendon ve bağ kalınlıklarını araştıran çalışma yoktur. AV'li hastalarda entezit varlığını araştırmak ve alt ekstremite tendon ve bağ kalınlıklarını değerlendirmek.

Gereç ve Yöntem: Çalışmaya AV tanılı 30 hasta ve 18 sağlıklı katılımcı dahil edildi. Akne şiddeti Global Acne Grading System (GAGS) ile belirlendi. Glasgow Ultrasonografik Entezit Skorlama Sistemine (GUESS) göre tek bir radyolog ultrasonografik değerlendirme yaptı. Ölçümler bilateral alt ekstremite kuadriseps tendonları, patellar tendonlar, aşil tendonları ve plantar fasyalardan yapıldı.

Bulgular: Gruplar arasında yaş, vücut kitle indeksi, alkol kullanımı ve sigara kullanımı benzerdi. GUESS skoru her iki grupta benzerdi. AV'li hastalarda dominant ve nondominant bacaklarda proksimal patellar ligaman, distal patellar ligaman, aşil tendonu ve plantar fasya kalınlıkları anlamlı olarak artmıştı ($p<0.05$).

Sonuç: Bu çalışma AV'nin bacak tendon ve bağ kalınlıklarında artışa yol açabileceğini düşündürmektedir.

Anahtar Kelimeler: Akne vulgaris, entezit, GUESS skor

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INTRODUCTION

Acne vulgaris (AV) is a multifactorial disease which affects pilosebaceous unit and 85% of the young population and is most common in adolescents (1). Abnormal follicular keratinization, excessive sebum production, bacterial colonization of Propionibacterium acnes (P. acnes) are involved in the pathogenesis of AV. It is believed that p. acnes are involved in the information of the inflammatory response (1). P. acnes activates the CD4+ lymphocytes and Toll like receptor-2 (TLR-2) on the monocytes by damaging the follicular wall (1). Thus IL-8 and similar proinflammatory cytokines are released. Also, other cytokines such as IL-1α, IL-1β and IL-17 are also released (1). In some studies, it was shown that p. acnes is a powerful stimulant of CD4+ T cells for releasing IFN-γ and IL-17 (2). Additionally, in biopsies of inflammatory acne lesions, IL-17 + cells were found in the perifollicular infiltrate. Therefore, it was thought that acne vulgaris may be a Th-17- related disease (2). It is known that the cytokines IL-17, IL-22, IL-23 and TNF- α play an active role in the formation mechanism of enthesis (3). The presence of enthesitis has also been shown in some syndromes accompanied by acne vulgaris such as SAPHO, psoriasis and Behcet's disease (4). So patients with AV may be susceptible to the development of enthesis. We aimed to evaluate the presence of enthesitis and the measurement of tendon and ligament thicknesses in legs in patients with AV in this study.

MATERIAL AND METHOD

The study was planned as randomized controlled study. This study was carried out with the permission of Hitit University, Clinical Researches Ethic Committee (Date: 11.12.2019, Desicion No: 131). Among the participants with AV who applied to the dermatology outpatient clinic, those with a single line were included in the study. Thirty patients who admitted to Dermatology clinic with a diagnosis of AV and eighteen healthy controls, were included to the study (5). The number of participants was determined by power analysis with 80% power and 0.5% standard error (5). Participants with concominant rheumatic and neurological diseases, psoriasis, acne rosacea, history of trauma, orthopedic surgery, other systemic diseases such as diabetes mellitus, hypothyroidism and hyperthyroidism, obese participants were excluded. Demographic and clinical characteristics, patients' acne type, duration and medications were recorded.

Acne severity was evaluated with the Global Acne Grading System (GAGS) (6). It divides the face, chest, and upper back into 6 regions: the forehead, right/left cheek, nose, chin and torso. Comedos (1 point), papules (2 points), pustules (3 points), and nodules (4 points) record. Absence of a lesion has a score of 0 points. The local score for each anatomic area is determined by multiplying the score of the most severe lesion by an area factor (one-three).The local scores of the 6 regions are summed to obtain the total score. Acne severity is graded as non (0 points), mild (1-18 points), moderate (19-30 points) severe (31-38 points) and very severe (total score >38 points) (7).

Ultrasonographic Measurement

A single radiologist, who had considerable experience on musculoskeletal ultrasonography (US) and blinded to the participant's group assignment, performed ultrasonographic evaluation used a multi-frequency linear probe (5-12 MHz for knees and 12-18 for feet; Toshiba Applio 500). While obtaining images, a generous amount of water-soluble gel was applied between the transducer and the skin to aid acoustic coupling and to avoid compression or deformation of the muscle fibres. Ultrasonographic measurement was performed after a period of rest 30 minutes. US grey scale was used for tendon thickness, echogenity calcifications, enthesophytes, bursitis and erosions. Glasgow Ultrasonographic Enthesitis Scoring System (GUESS) was used for evaluating the enthesis areas (8). Examination of the superior pole of the patella (the insertion of quadriceps tendon), the inferior pole of the patella (the origin of patellar ligament), and the patellar ligament insertion at the tibial tuberosity was performed with the participants in the supine position with the knee flexed at 30 degrees (8). The Achilles tendon and the plantar aponeurosis were performed with the participants lying prone with the feet hanging over the edge of the examination table at 90 degrees of flexion (8). For each areas with an increase of tendon thickness, the presence of enthesophyte, bursitis or erosion was scored as 1 point. The minimum total score was 0 point and the maximum total score was 36.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 16.0 program for Windows. Visual and analytical methods were used to determine whether or not variables were normally distributed. Continuous values were expressed as mean ± standard deviation (SD). Chi Square test and Fisher Exact test were used to compare nominal values. Independent sample t-test was used for comparison of normally distributed data, and the Mann-Whitney U test was used for comparison of non-normally distributed data. Pearson and Spearman correlation coefficients was used to investigate correlation between patient's characteristics and clinical parameters. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Age, body mass index, alcohol usage and smoking were similar between groups (**Table 1**). Disease characteristics of acne vulgaris were summerized in **Table 2**. Acne vulgaris duration was 4±2.30 years in patients with acne vulgaris. Previously, 29 patients used topical treatment, 8 patients used systemic antibiotherapy and 3 patients used isotretinoin (**Table 2**). There was non-inflammatory acne vulgaris in 16 patients with AV and inflammatory acne vulgaris in 30 patients with AV (**Table 2**). GAGS score was 19.5±5.78 in patients wİth AV (**Table 2**).

Table 1. Demographic and clinical characteristics of participants

	Patients with AV n= 30	Control group n= 18	p value
Age (years)	20 (19-22)	22.5 (20-25)	0.051
Weights (kg)	58.8±7.43	62.27±5.92	0.095
Heights (cm)	163.5±6.25	165.8±4.22	0.159
Body mass index	21.98±2.5	22.58±1.43	0.298
Alcohol use (n, %)	0	1 (5.6%)	0.375
Smoking (n,%)	3 (10%)	4 (22.2%)	0.400
Guess score	0 (0-0)	0 (0-0)	0.366

AV: Acne Vulgaris, GUESS: Glasgow Ultrasound Enthesitis Scoring System)
Data are presented as the mean ± standart deviation for data normally distributed or median (25-75%) for data not normally distributed. p< 0,05

Table 2. Disease characteristics of acne vulgaris patients

	Patients with acne vulgaris n= 30
Acne duration (year)	4±2.30
Patients received treatment (n, %)	28 (93.3%)
Types of treatment (n, %)	
Topical	29 (96.7%)
Systemic antibiotherapy	8 (26.7%)
isotretinoin	3 (10%)
Types of acne vulgaris (n,%)	
Non-inflammatory	16 (53.3%)
İnflammatory	30 (100%)
Nodulocyctic	0
Truncal	0
Presence of scar (n,%)	30 (100%)
Types of scar (n, %)	
Macule	16 (53.3%)
Atrophic	14 (46.7%)
Hypertrophic	0
GAGS Score	19.5±5.78
Acne severity (n, %)	
Non	0
Mild	10 (33.3%)
Moderate	20 (66.7%)
Severe	0
Very severe	0

GAGS: Global Acne Grading System, Data are presented as the mean ± standart deviation for data normally distributed or n (%) for categoric values.

All participants were right dominancy. GUESS score was similar in both group (**Table 1**). Proximal patellar ligaments, distal patellar ligaments, Achilles tendons and plantar fascias thicknesses were significantly increased bilaterally in AV patients (**Table 3**, **4**). There was no significant difffence in quadriceps tendons thicknesses between groups in bilateral legs (**Table 3**, **4**). A significant correlation was found between quadriceps tendon thickness and weight in dominant and non dominant leg in AV patients(r=0.497 p<0.001 and r=0.398 p<0.05 respectively). There was no correlation between age, weight, height, body mass index and other tendon thicknesses in AV patients (**Table 5**). A significant correlation was found between weight, height, body mass index and quadriceps tendon thickness in dominant and non-dominant legs in healthy controls (**Table 6**). Also, in dominant leg there was a correlation between height and proximal patellar ligament thickness in healthy controls (r=0.531 p<0.05).

Table 3. Tendon thicknesses and GUESS scores of the participants in dominant leg.

	Patients with AV n= 30	Control group n= 18	p value
Quadriceps tendon thickness (mm)	5.22±0.67	4.86±0.60	0.068
Proximal patellar ligament thickness (mm)	3.36±0.38	2.95±0.53	0.003
Distal patellar ligament thickness (mm)	3.50 (3.35-3.72)	3 (2.67-3.35)	0.001
Achilles tendon thickness (mm)	3.98±0.41	3.60±0.53	0.008
Plantar fascia thickness (mm)	2.96±0.42	2.49±0.46	0.001

AV: Acne Vulgaris, Data are presented as the mean ± standart deviation for data normally distributed or median (25-75%) for data not normally distributed. p< 0,05

Table 4. Tendon thicknesses and GUESS scores of the participants in non-dominant leg.

	Patients with AV n= 30	Control group n= 18	p value
Quadriceps tendon thickness (mm)	5.19±0.67	4.82±0.60	0.063
Proximal patellar ligament thickness (mm)	3.31±0.39	2.91±0.52	0.005
Distal patellar ligament thickness (mm)	3.4 (3.17-3.62)	3 (2.67-3.35)	0.003
Achilles tendon thickness (mm)	3.98±0.41	3.57±0.50	0.004
Plantar fascia thickness (mm)	2.96±0.41	2.5±0.44	0.001

AV: Acne Vulgaris, Data are presented as the mean ± standart deviation for data normally distributed or median (25-75%) for data not normally distributed. p< 0,05

Table 5. Correlation between age, height, weight, body mass index and tendon thicknesses in patients with AV.

	Age	Height	Weight	Body mass index
Dominant leg				
Quadriceps tendon thickness	-0.180[1]	0.178[2]	0.497**[2]	0.358[2]
Proximal patellar ligament thickness	-0.185[1]	0.255[2]	0.270[2]	0.148[2]
Distal patellar ligament thickness	-0.096[1]	0.104[1]	0.266[1]	0.147[1]
Achilles tendon thickness	-0.011[1]	0.271[2]	0.214[2]	0.129[2]
Plantar fascia thickness	0.012[1]	0.085[2]	0.139[2]	0.111[2]
Non-dominant leg				
Quadriceps tendon thickness	-0.180[1]	0.151[2]	0.398*[2]	0.339[2]
Proximal patellar ligament thickness	-0.244[1]	0.215[2]	0.199[2]	0.065[2]
Distal patellar ligament thickness	-0.317[1]	0.104[1]	0.266[1]	0.147[1]
Achilles tendon thickness	-0.017[1]	0.219[2]	0.253[2]	0.108[2]
Plantar fascia thickness	0.028[1]	0.089[2]	0.169[2]	0.120[2]

1: Spearman, 2: Pearson, *: p<0.05, **:p <0.001

Table 6. Correlation between age, height, weight, body mass index and tendon thicknesses in healthy controls.

	Age	Height	Weight	Body mass index
Dominant leg				
Quadriceps tendon thickness	-0.086[1]	0655**[2]	0.640**[2]	0.507*[2]
Proximal patellar ligament thickness	-0.340[1]	0.531*[2]	0.340[2]	0.143[2]
Distal patellar ligament thickness	-0.369[1]	0.366[1]	0.209[1]	-0.59[1]
Achilles tendon thickness	-0.351[1]	0.302[2]	0.071[2]	-0.118[2]
Plantar fascia thickness	-0.168[1]	0.379[2]	0.307[2]	-0.201[2]
Non-dominant leg				
Quadriceps tendon thickness	-0.114[1]	0.649**[2]	0.630**[2]	0.494*[2]
Proximal patellar ligament thickness	-0.345[1]	0.507*[2]	0.321[2]	0.134[2]
Distal patellar ligament thickness	-0.367[1]	0.398[1]	0.251[1]	-0.019[1]
Achilles tendon thickness	-0.287[1]	0.282[2]	0.066[2]	-0.108[2]
Plantar fascia thickness	-0.157[1]	0.353[2]	0.257[2]	0.146[2]

1: Spearman, 2: Pearson, *: p<0.05, **:p <0.001

DISCUSSION

In this study, some lower extremity tendon and ligament thicknesses were found increased in bilateral legs in AV patients compared to healthy controls. We did not found increased GUESS score in AV patients. Additionally, we did not found any enthesitis in patients with acne vulgaris. This is the first study which invastigated the relationship between acne vulgaris and the presence of enthesitis and tendons and ligaments thicknesses in lower extremities in the literature.

The causes of enthesopathy is the inflammation of tendons, ligaments or capsules' insertion into the bone. It is one of the most common findings in patients with spondyloarthritis. In murine models, TNFα or IL-23/17 pathway dysregulation was showed which leads to inflammation and plays important role for enthesitis in spondyloarthropathy pathogenesis (9-12). Recent studies showed that anti-IL-17A therapy is effective in ankylosing spondylitis (13,14).

In the literature, there are some studies demonstrating that the presence of IL-17A+ cells, in acne lesions that appear clinically early. Activations of cytokines, chemokines and antimicrobial peptides are typical for the Th17/IL-17 pathway (15). Th1, Th17 and CD8+ activation and neutrophil attraction with IL-17-related chemokine production may be important factors in the pathogenesis of AV (15) . Ebrahim et al. (16) showed higher serum IL-17 level in AV patients and it was associated with disease severity. They thought that IL-17 could be a potential prognostic predictor for severity and scarring in AV.

Since we know that IL-17 plays a role in both AV and enthesopathy pathogenesis, we found that it is valuable to evaluate the enthesis site by ultrasonography in patients with AV. In our study, proximal patellar tendons, distal patellar tendons, Achilles tendons and plantar fascias' thicknesses were significantly increased in both extremity in AV patients compared to healthy controls. But we found similar GUESS scores between AV patients and healthy controls. So we could comment that AV may be a predisposing factor for enthesitis development. In our study, all participant were young adults. Also, all patients had mild or moderate acne severity. If patients had a long duration of AV or had severe AV, perhaps enthesitis could be detected. For invastigating the relationship between AV and enthesopathy, prospective controlled studies are needed.

Hatemi et al. (17) found that Behçet's disease with acne and arthritis had increased presence of enthesopathy compared to Behçet's disease without arthritis. So acne vulgaris may contribute to the development of enthesopathy. Also there are some studies showing that the using isotretinoin can cause the development of sacroileitis (18). Altan et al. (19) invastigated the isotiretinoin-related spondyloarthropathy symptoms and they found unilateral Achilles enthesopathy in 3 patients and unilateral sacroileitis in 1 patient. They found the spondyloarthropathy findings in 23.1% of the patients who used isotretinoin. If AV is predisposing

to the development of enthesopathy, it will be valuable to evaluate the presence of enthesopathy when starting isotretinoin in patients with AV. In our study, there were only 3 patients with acne vulgaris who used isotretinoin before. In these patients, we did not found any enthesopathy.

This study has some limitations. Because of the cross-sectional design of the study, the changes of tendons and ligaments thicknesses in course of time remains unclear. Also we did not evaluate the physical activity levels of the participants. Tendon and ligament thickness can be affected by exercise and physical activity. In case-control studies, including more than one participant in the control group for each participant in the case group will increase the power of the study. Therefore, the small number of participants in the control group can be accepted as one of the limitation of the study.

CONCLUSION

This study suggest that AV may lead to increase in thickness of leg tendons and ligaments. To our knowledge, this is the first study to examine ultrasonographic findings of lower extremities' tendons and ligaments among the AV patients. Further prospective studies are needed that examine the relationship between Acne vulgaris and enthesopathies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University, Clinical Researches Ethics Committee (Date: 11.12.2019, Desicion No: 131). This study was registered to ClinicalTrials.gov with the number of NCT04224597.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Aksaç SE, Bilgili SG, Yavuz İH, Yavuz GÖ. Akne vulgariste etyopatogenez. Van Tıp Dergisi 2018; 25: 260-7.
2. Agak GW, Kao S, Quyang K, et al. Phenotype and antimicrobial activity of Th17 cells induced by Propionibacterium acnes strains associated with healthy and acne skin. J Investigative Dermatol 2018; 138: 316-24.
3. Watad A, Cuthbert RJ, Amital H, McGonagle D. Enthesitis: much more than focal insertion point inflammation. Current Rheumatology Reports 2018; 20: 41.
4. Huhn CK, Schauer F, Schempp CM, Venhoff N, Finzel S. Skin inflammation associated with arthritis, synovitis and enthesitis. Part 1: psoriatic arthritis, SAPHO syndrome, Still's disease, Behçet's disease. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2019; 17: 43-64.
5. Ebstein E, Coustet B, Masson Behar V, et al. Enthesopathy in rheumatoid arthritis and spondyloarthritis: An ultrasound study. Joint Bone Spine 2018; 85: 577-81.
6. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol 1997; 36: 416–8.
7. Hacivelioglu S, Güngör ANC, Gencer M, et al. Acne severity and the Global Acne Grading System in polycystic ovary syndrome. Int J Gynaecol Obstet 2013; 123: 33-6.
8. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock R, al. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis 2002; 61: 905–10.
9. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. The Lancet 1998; 352: 1137–40.
10. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4−CD8− entheseal resident T cells. Nat Med 2012; 18: 1069–76.
11. Lories RJU, Derese I, de Bari C, et al. Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondylarthritis. Arthritis Rheum 2007; 56: 489–97.
12. Armaka M, Apostolaki M, Jacques P, Kontoyiannis DL, Elewaut D, Kollias G. Mesenchymal cell targeting by TNF as a common pathogenic principle in chronic inflammatory joint and intestinal diseases. J Exp Med 2008; 205: 331–7.
13. Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015; 373: 2534–48.
14. Dubash S, Bridgewood C, McGonagle D, Marzo-Ortega H. The advent of IL-17A blockade in ankylosing spondylitis: secukinumab, ixekizumab and beyond. Expert Rev Clin Immunol 2019; 15: 123–34.
15. Kelhälä HL, Palatsi R, Fhyrquist N, et al. IL-17/Th17 pathway is activated in acne lesions. PLoS One 2014; 9: e105238.
16. Ebrahim AA, Mustafa AI, El-Abd AM. Serum interleukin-17 as a novel biomarker in patients with acne vulgaris. J Cosmet Dermatol. 2019; 18: 1975-9.
17. Hatemi G, Fresko I, Tascilar K, Yazici H. Increased enthesopathy among Behçet's syndrome patients with acne and arthritis: an ultrasonography study. Arthritis Rheum 2008; 58: 1539-45.
18. Coskun BN, Yagiz B, Pehlivan Y, Dalkilic E. Isotretinoin-induced sacroiliitis in patients with hidradenitis suppurativa: a case-based review. Rheumatol Int 2019; 39: 2159-65.
19. Alkan S, Kayiran N, Zengin O, et al. Isotretinoin-induced Spondyloarthropathy-related Symptoms: A Prospective Study. J Rheumatol 2015; 42: 2106-9.